Surgical and Oncologic Outcomes After Major Liver Surgery and Extended Hemihepatectomy for Colorectal Liver Metastases

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Abstract

Extensive liver surgery for colorectal liver metastases (CRLM) is frequently performed, but data on the outcomes of these complex surgical procedures are scarce. Here we report surgical and oncologic outcomes for 117 patients who underwent major liver surgery at a Dutch tertiary referral center. Major hepatic resection is associated with considerable postoperative morbidity and mortality, but it can provide significant long-term survival for patients with CRLM.

Purpose: To determine the surgical and oncologic outcomes after major liver surgery for colorectal liver metastases (CRLM) at a Dutch University Hospital. **Patients and Methods:** Consecutive patients with CRLM who had undergone major liver resection, defined as $\geq$ 4 liver segments, between January 2000 and December 2015 were identified from a prospectively maintained database. **Results:** Major liver surgery was performed in 117 patients. Of these, 26 patients had undergone formal extended left or right hemihepatectomy. Ninety-day postoperative mortality was 8%. Major postoperative complications occurred in 27% of patients; these adverse events were more common in the extended hemihepatectomy group. Median disease-free survival was 11 months and median overall survival 44 months. **Conclusion:** Major liver surgery, including formal extended hemihepatectomy, is associated with significant operative morbidity and mortality but can confer prolonged overall survival for patients with CRLM.

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Introduction

Complete surgical resection is the only curative treatment option for patients with colorectal liver metastases (CRLM). If left untreated, median survival after diagnosis of CRLM is less than 1 year.[1] With a 5-year survival rate of up to 50%, surgical resection significantly improves the prognosis of these patients.[2,3] The limited criteria for partial liver resection (presence of a maximum of 3 metastases, absence of additional extrahepatic disease, and resection margin $>$ 10 mm[4]) have largely been abandoned. Resectability is now defined as the ability to surgically remove all visible liver metastases with tumor-free margins while preserving adequate future liver remnant volume (FLRV) with sufficient vascular supply and biliary drainage.[3] Advances in surgical technique, use of preoperative portal vein embolization (PVE) to induce compensatory hypertrophy for improvement of FLRV, and effectiveness of neoadjuvant chemotherapeutic regimens have increased the number of patients eligible for resection.[5-7] Nevertheless, only 20% to 30% of patients with liver metastases are potential candidates for resection.[3,8]

With the expanding indications for liver resection in patients with CRLM, major hepatectomy, defined as resection of 4 or more liver segments[9] and extended hemihepatectomies (ie, right or left trisectionectomy[10]), are executed in most hepatobiliary tertiary referral centers. Major liver resection remains a high-risk procedure, however. The incidence of complications has been correlated to the extent of liver surgery, with severe complications reported in up to 40% of patients undergoing major liver resection for CRLM.[11-13] Despite improvement in perioperative management, the mortality associated with extensive liver surgery has remained unchanged over the past 20 years.[14] Careful appraisal of the benefits is therefore

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essential. Data on the long-term outcomes of major liver surgery are scarce, however, with only a few available reports from high-volume centers that specialize in liver surgery.

Here we present the surgical and oncologic outcomes of major liver resections, including extended hemihepatectomies, in patients with CRLM from a large single-center cohort.

Patients and Methods

Study Population

From a prospective database, we identified patients undergoing major liver surgery for CRLM with curative intent between January 2000 and December 2015 at the University Medical Center Utrecht, the Netherlands. Major liver surgery is defined as resection of 4 or more liver segments.[9]

Data Collection

Demographic and clinicopathologic characteristics, including age, sex, primary tumor characteristics, chemotherapeutic treatment, PVE, number of CRLMs, type of liver surgery, resection margins, postoperative mortality, disease-free survival (DFS), and overall survival (OS) were collected prospectively.

Synchronous liver metastases were defined as metastases detected before or during primary tumor resection. The postoperative mortality rate was assessed at 90 days after surgery. DFS and OS were calculated from the date of hepatic resection to the date of first recurrence detected with radiologic imaging and death. If there were no events, patients were censored at last follow-up. Patients whose extrahepatic disease was not resected or who had a primary tumor still in situ were excluded from the DFS analyses but included in the OS analyses.

Data on duration of surgery, amount of blood loss, duration of hospital and intensive care unit stay, and postoperative morbidity were collected retrospectively. Postoperative complications were independently graded according to the Clavien-Dindo classification[15] by 2 researchers (I.U. and J.J.) on the basis of information available from electronic medical records. In case of disagreement, a third opinion (J.H.) was decisive. Only major complications (Clavien-Dindo grades III to V) that occurred before first hospital discharge were recorded.

Hepatic Resection

Routine preoperative imaging included liver contrast-enhanced 3-phase computed tomography and thoracoabdominal spiral computed tomographic scan to assess resectability, FLRV, and extrahepatic metastases. Magnetic resonance imaging of the liver or positron emission tomography were performed as indicated. Portal vein embolization was carried out before surgery to improve FLRV if indicated.

All resections were performed with curative intent by 4 expert hepatic surgeons. After laparotomy, the abdomen was explored, and intraoperative ultrasound was performed to determine the extent and resectability of the metastases. Parenchymal transection was performed with an ultrasonic dissector. To minimize blood loss, central venous pressure was maintained below 5 mm Hg. Intermittent portal triad clamping (Pringle maneuver) was applied if the surgeons expected excessive blood loss.[16] Hemostasis and biliostasis were achieved with bipolar cautery coagulation, clips, or ligation.

The Brisbane 2000 terminology[10] was used to describe the type of liver resections. Extended right hemihepatectomy (or right trisectionectomy) requires en bloc resection of segment IV (a, b, or both) in addition to right hemihepatectomy with or without caudate resection. Extended left hemihepatectomy (or left trisectionectomy) is defined as left hepatectomy (segments I, II, III, and IV) plus segments V and VIII. The resection specimen was analyzed by an experienced pathologist to assess resection margins. A resection is denoted R0 if all margins are free of tumor, R1 if there is microscopic invasion of the resection surface, and R2 if the resection is macroscopically not radical.

Statistical Analysis

Statistical analyses were performed by SPSS 20 (IBM SPSS, Chicago, IL). The Pearson chi-square test was used to compare differences in discrete or categorical data, whereas continuous data were analyzed with the Mann-Whitney *U* test. DFS and OS curves were generated using the Kaplan-Meier method; differences between survival curves were assessed by log rank test. A level of $P < .05$ was considered statistically significant.

Results

Patient and Oncologic Characteristics

Between January 2000 and December 2015, a total of 543 partial hepatectomies were performed, of which 312 were performed for CRLM. Repeat hepatectomies (n = 33), 2-stage hepatectomies (n = 8), and resections in combination with hyperthermic intraperitoneal chemotherapy (n = 1) were excluded from this analysis, resulting in a cohort of 270 liver resections for CRLM. Of these, 117 (43%) were major hepatic resections. Patient and tumor characteristics are listed in Table 1. The median age at time of liver surgery was 63 years; 66% of patients were male. The majority of primary tumors were located in the sigmoid and rectum. Half of the patients presented with synchronous CRLM; 23 patients (9%) had simultaneous extrahepatic disease. Neoadjuvant chemotherapy was administered to 29% of all patients, more often before major resection than minor hepatectomy ($P = .014$). Patients with synchronous CRLM had more often received neoadjuvant chemotherapy ($P < .001$). PVE to increase FLRV before liver resection was performed in 12 patients.

Surgical Outcomes of Major Hepatectomy for CRLM

Of the 117 major liver resections, 26 procedures were formal extended hemihepatectomies (right, n = 22; left, n = 4; Table 2). Radiofrequency ablation in addition to major surgery was performed in 9 patients, and liver surgery was combined with resection of extrahepatic disease in 3 of 8 patients. The majority of patients with synchronous CRLM were treated in the traditional (primary tumor first) order; the reversed, or liver-first, procedure, in which CRLM are resected before the primary tumor, was used in 9 patients, of whom 5 underwent an extended hemihepatectomy. The R0 resection rate was 90% (Table 2).

Major postoperative complications (Clavien-Dindo grades III to V) occurred in 27% of patients who underwent major resection. An overview of these complications is shown in Table 3. The most common adverse event was pleural effusion requiring

Table 1 Patient and Oncologic Characteristics

Characteristic	All Resections (n = 270)	Minor Resections (n = 153)	Major Resections (n = 117)
Age, years	63 (32-85)	64 (37-85)	62 (32-83)
Male gender	177 (66)	98 (65)	79 (67)
Primary Tumor			
Location[a]			
Cecum + right hemicolon	56 (21)	37 (24)	19 (17)
Left hemicolon	19 (7)	6 (4)	13 (11)
(Recto)sigmoid	93 (35)	55 (36)	38 (33)
Rectum	97 (37)	52 (34)	45 (39)
T stage T3/T4[b]	215 (88)	122 (89)	93 (88)
N status N1/N2[c]	155 (63)	84 (61)	71 (65)
Hepatic Metastases			
Number	2 (1-20)	1 (1-10)	2 (1-20)
Synchronous metastases	136 (50)	71 (46)	65 (56)
Concomitant extrahepatic disease[d]	23 (9)	15 (10)	8 (7)
Neoadjuvant chemotherapy[e]	78 (29)	33 (22)	45 (39)
Portal vein embolization	12 (4)	2 (1)	10 (9)
ASA Physical Status Classification[f]			
ASA 1	45 (25)	27 (27)	18 (23)
ASA 2	119 (67)	66 (65)	53 (69)
ASA 3	15 (8)	9 (9)	6 (8)

Data are presented as median (range) or n (%). Data are available for: [a]265, [b]243, [c]247, [d]266, [e]254, and [f]179 patients.
Abbreviation: ASA = American Society of Anesthesiologists.

thoracocentesis. Major complications were more common after formal extended hemihepatectomy compared to other major resections (46% vs. 21% complication rate, respectively, $P = .01$). Patients treated with neoadjuvant chemotherapy more often experienced major complications, but this difference was not statistically significant (36% vs. 21% respectively, $P = .08$). The occurrence of major complications significantly prolonged median intensive care unit and hospital stay. Of the discharged patients, 15% were readmitted to the hospital for unresolved or new complications.

The 90-day postoperative mortality rate after major liver surgery was 8% compared to 2% in the minor resection group ($P = .02$). Causes of death after major resection were as follows: hepatic failure (n = 2), multiorgan failure (n = 2), pancreatitis (n = 1), acute respiratory distress syndrome (n = 2), pulmonary embolism (n = 1), and intra-abdominal hemorrhage (n = 1).

Recurrence and OS

Median follow-up after major hepatectomy was 22.5 months (range, 0.3-132 months). The median DFS was 11 months (95% confidence interval [CI], 7.3-15.3 months). One- and 3-year DFS were 49% and 21%, respectively. Median OS was 44 months (95% CI, 28.2-60.3 months). One-, 3-, and 5-year OS rates were 87%, 59%, and 40%, respectively. Patients who had received neoadjuvant therapy had a shorter median OS (35 months; 95% CI, 24-46 months), versus 73 months (95% CI, 32-114 months) without chemotherapy ($P = .02$). There were no significant differences in DFS and OS between minor and major liver resections (Figure 1).

Discussion

Extensive liver resections are frequently being performed for CRLM; however, data on the short- and long-term oncologic outcomes of these highly complex surgical procedures are scarce and are almost exclusively reported by a few high-volume centers. This leaves several vital questions regarding the potential risks and benefits of these procedures unanswered, encumbering patient counseling and clinical decision making. Here we present data on surgical and oncologic outcomes for 117 patients with metastatic CRLM who underwent major liver resection (4 or more liver segments) at a Dutch tertiary referral center.

Short-Term Outcomes

It has been shown that resection of 4 or more segments significantly increases the risk of postoperative morbidity and mortality compared to less extensive resections.[9,11,14] High complication rates of major liver surgery have been reported by, eg, Konopke et al[11] (37%) and van Dam et al[12] (33%). In our cohort, 27% of the patients experienced grade III or higher postoperative complications. The distribution of the observed complications corresponds well with the complications found in a recent study on predictors for complications after hemihepatectomy.[17] Patients who underwent extended hemihepatectomy had significantly more complications than patient undergoing other major resections, which should be taken into account when selecting patients for resection. Postoperative complications led to death in 9 patients (8%) in this cohort, which is comparable with other studies on major liver surgery for

Table 2 Perioperative Characteristics

Operative Characteristic	All Resections (n = 270)	Minor Resections (n = 153)	Major Resections (n = 117)
Type of Liver Resection			
Extended left hepatectomy	4 (2)	0 (0)	4 (3)
Extended right hepatectomy	22 (8)	0 (0)	22 (19)
Left hemihepatectomy	24 (9)	0 (0)	24 (21)
Right hemihepatectomy	64 (24)	0 (0)	64 (55)
Multisegmentectomy (≥4)	3 (1)	0 (0)	3 (3)
Three segments	16 (6)	16 (11)	0 (0)
Two segments	42 (16)	42 (28)	0 (0)
One segment	43 (16)	43 (28)	0 (0)
Wedge resection	52 (19)	52 (34)	0 (0)
Combined primary + liver resection	5 (2)	5 (3)	0 (0)
Liver-first procedure	13 (5)	4 (3)	9 (8)
Concomitant radiofrequency ablation	29 (11)	20 (13)	9 (8)
Surgery duration, minutes[a]	220 (70-540)	180 (70-420)	250 (120-540)
Pringle maneuver[b]	139 (52)	77 (63)	62 (55)
Blood loss, mL[c]	600 (0-12,150)	475 (0-11,000)	900 (100-12,150)
Postoperative Course			
Hospital stay, days	9 (3-74)	8 (3-74)	12 (4-67)
ICU stay, days	1 (0-55)	1 (0-54)	1 (0-55)
Postoperative deaths	12 (4)	3 (2)	9 (8)
Readmissions	30 (11)	13 (8)	17 (15)
Resection Margins			
R0	243 (90)	138 (90)	105 (90)
R1	26 (10)	15 (10)	11 (9)
R2	1 (0)	0 (0)	1 (1)

Data are presented as median (range) or n (%). Data are available for: [a]265, [b]235, and [c]183 patients.
Abbreviation: ICU = intensive care unit.

CRLM, with reported mortality rates between 0% and 10%.[9,13,18-21] Over the past 2 decades, Kingham et al[14] noted a remarkable decline in postoperative complications and deaths coinciding with a decrease in the number of major resections performed. Preservation of hepatic parenchyma, by combining resection with radiofrequency ablation or by expanding FLRV with PVE, could thus limit postoperative morbidity and mortality.

Long-Term Outcomes

Few studies have presented survival data on major liver surgery for CRLM, defined as resection of 4 or more liver segments. Five-year DFS ranged from 4% to 25.5%; 5-year OS was reported between 25% and 38.7%.[18,19,22-24] Our survival results (3-year DFS 21% and 5-year OS 40%) are in line with these reports. In previous studies, major hepatectomy patients appear to have a shorter survival compared to patients undergoing minor resection for CRLM.[18,22] Presumably this is due to a higher tumor burden, considering that the number of metastases significantly influences OS.[1] We did not observe differences in DFS or OS between minor and major resections in our cohort; however, we did see a correlation between the number of metastases and survival outcomes (data not shown). The improvement in OS compared to palliative chemotherapy (median OS, 20-24 months[25]) indicates that surgical resection, even if major or extended hepatectomy is required, is the preferred treatment option for CRLM if possible. Despite the fairly positive OS rate, DFS remains low in this study, even though R0 resection was achieved in the majority of patients.

Preoperative Chemotherapy

Neoadjuvant chemotherapy is considered for downsizing initially unresectable CRLM; up to 23% of patients with initially unresectable metastases can undergo macroscopic curative resection after neoadjuvant therapy.[6] Preoperative chemotherapy is also used in patients with resectable disease to reduce the chances of postoperative relapse, although recently no significant survival benefit was found with the addition of perioperative chemotherapy (FOLFOX4) compared to surgery alone for patients with resectable liver metastases.[2] Unfortunately, preoperative chemotherapy comes at a cost: chemotherapy-induced hepatic injury increases the risk of postoperative complications.[26] In our cohort, we observed a trend toward increased morbidity associated with neoadjuvant chemotherapy, but this was not statistically significant. We did notice a shorter OS in patients who had received preoperative chemotherapy. Cases were not matched, however, and we did not correct

Table 3 Specification Grade 3 or Higher Postoperative Complications

Complication	Incidence Grade III-V
Hepatic Complications	
Hepatic failure	6
Hepatic hemorrhage	1
Hepatic necrosis	1
Perforation bile duct	4
Bile duct stenosis	1
Pulmonary Complications	
Pleural effusion	15
Respiratory insufficiency	5
Lung infection	1
Pneumothorax	2
Other Complications	
Intra-abdominal abscess	4
Peritoneal infection	3
Thromboembolic event	4
Wound complication	3
Multiorgan failure	2
Acute renal failure	1
Sepsis e causa ignota	1
Intra-abdominal hemorrhage	1
Pancreatitis	1
Gastric ulcer bleeding	1
Pericardial tamponade	1
Procedural complication: colon perforation	1

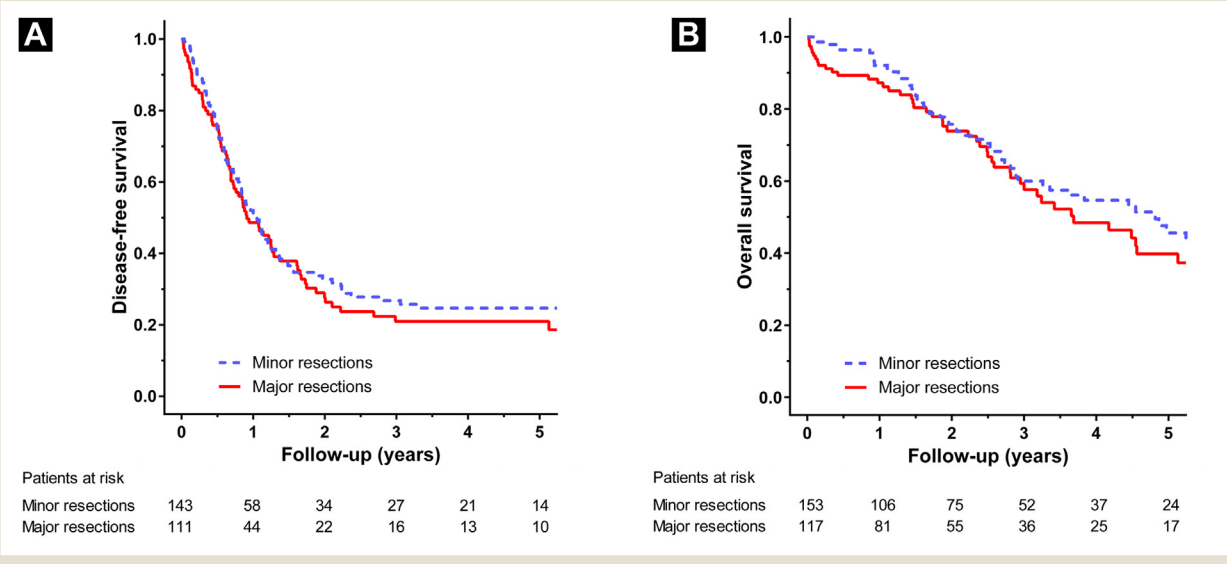
for potential confounding variables. A possible explanation for the shorter OS is that these patients presented with initially unresectable metastases, reflecting a more extensive tumor spread compared to patients who did not require neoadjuvant chemotherapy. Indeed, patients with primarily resectable disease had better OS than patients with down-staged metastases in a large series of CRLM.[27] Nevertheless, survival outcome of resection after conversion chemotherapy is better compared to survival after chemotherapy alone.[28]

Even though this study is limited by the relatively small sample size with patients from a single institution, and even though our findings are from retrospective analysis of prospectively collected data, the results of this study confirm that major hepatic resection and formal extended hemihepatectomy for the treatment of CRLM can provide significant long-term survival. As a result of the complexity of the procedure, major liver surgery is associated with relatively high postoperative morbidity and mortality. Determination of the appropriate treatment sequence for synchronous liver metastases, increasing efforts to perform parenchymal-sparing resections, and further improvement in selection of patients suitable for major hepatic resection should reduce the complication rate and ameliorate DFS and OS.

Clinical Practice Points

- The results of this study confirm that major hepatic resection, including extended hemihepatectomy, can provide significant long-term survival for patients with CRLM.
- The improvement in median OS after extensive liver surgery (40 months in our study), compared to survival rates reported for palliative chemotherapy (20-24 months), indicates that major or extended hepatectomy should definitely be considered as a treatment option for CRLM.
- Major liver surgery remains associated with considerable perioperative morbidity and mortality. Careful patient selection and increasing efforts to perform parenchymal-sparing resections should reduce the complication rate and further ameliorate DFS and OS.

Figure 1 Disease-Free (A) and Overall Survival (B) After Minor or Major Hepatectomy for Colorectal Liver Metastases



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Disclosure

The authors have stated that they have no conflict of interest.

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